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Fracture Incidence in Ehlers-Danlos Syndrome – A Population-Based Case-Control Study

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Abstract

Background—The differential diagnosis of non-accidental injury during childhood includes medical conditions that predispose to skeletal fragility. Ehlers-Danlos syndrome (EDS) has been proposed as one such condition despite little objective evidence in the medical literature.

Objective—To investigate if EDS causes increased bone fragility during infancy and childhood.

Participants and Setting—Residents of an 8-county region in southern Minnesota using the *Rochester Epidemiology Project* (REP) medical records-linkage system.

Methods—This retrospective, population-based, case-control study identified subjects with EDS from 1976 – 2015 who had complete records for at least their first year of life. Validity of diagnosis was ascertained using the *2017 International Classification of the Ehlers-Danlos*

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Declaration of interest: none.

Syndromes. Records were reviewed for fracture diagnoses that were characterized by age, location, type and mechanism.

Results—Of 219 potential cases, 21 had complete records for the first year of life and sufficient evidence in the medical record to support an EDS diagnosis. Of these 21, there were 14 hypermobile, 2 classical, 4 vascular, and 1 arthrochalasia EDS subtypes. 11 of 21 EDS cases (52.4%) and 15 of 63 controls (23.8%) had one or more fractures during childhood. No fractures were identified in the first year of life. Comparing cases to controls, EDS was associated with having any fractures during childhood with an odds ratio of 3.4 (95% CI: 1.20 – 9.66).

Conclusions—We found no evidence that infants with common forms of EDS are predisposed to more frequent fractures. Ambulatory subjects with these EDS subtypes may have a higher incidence of fractures during childhood.

Keywords

Child Abuse; Infant; Ehlers-Danlos Syndrome; Fractures; Bone

INTRODUCTION

Child maltreatment is a leading cause of injury and death during childhood – it has been estimated that among U.S. children 0 – 17 years old, 1 in 10 will experience physical abuse by a caregiver sometime during childhood, with 5% experiencing physical abuse in the past year (Finkelhor, Turner, Shattuck, & Hamby, 2015). The most common manifestations of child physical abuse are bruising and fractures (Servaes et al., 2016). Differentiating accidental from non-accidental injuries requires evaluation of the reported mechanism of injury, developmental abilities of the child, injury characteristics, and careful consideration of potential underlying medical conditions that may mimic non-accidental injury.

One such condition is Ehlers-Danlos syndrome (EDS), which has been reported as one condition that may be occasionally misdiagnosed as child abuse (Roberts, Pope, Nicholls, & Narcisi, 1984; Wardinsky, Vizcarrondo, & Cruz, 1995). EDS is a heterogeneous group of inherited connective tissue disorders characterized by skin hyperelasticity and fragility, generalized joint hypermobility, and tissue, vascular and internal organ fragility (Malfait & De Paepe, 2014). EDS is felt to affect roughly 1/5000 persons. Currently, 13 EDS subtypes have been identified, the most common of which are the classic, hypermobility and vascular subtypes (Malfait et al., 2017).

Recently, several lay media articles (e.g. (McKim, 2015; Roldan, 2017) and a recent case series (Holick, Hossein-Nezhad, & Tabatabaei, 2017) have posited EDS as a reasonable alternative explanation rather than child abuse when an infant is found to have multiple unexplained fractures. However, whether EDS is associated with increased bone fragility that can be confused with abuse is controversial, as the evidence supporting such an association is limited, and consensus reports from medical genetics societies do not list abnormal predisposition to fracturing as a clinical manifestation of EDS, except for some rare EDS-Osteogenesis Imperfecta (OI) overlap syndromes (Malfait et al., 2017). Aside from the Holick et al. case series, no peer-reviewed literature supports the hypothesis that

subjects with the more common forms of EDS (hypermobility, classic, vascular) have increased fracture susceptibility during infancy or childhood (Shur & Carey, 2015). Because of the legitimate concerns about misdiagnosing an underlying medical condition as abuse or missing abuse by erroneously attributing fractures to a presumed connective tissue disorder, we investigated whether subjects with established EDS had evidence of increased bone fragility during childhood, and in particular during infancy.

METHODS

Study Sample, Eligibility and Design

We utilized data from the core 8-county (Olmsted, Dodge, Mower, Goodhue, Wabasha, Freeborn, Steele, and Waseca counties in Southeastern Minnesota) Rochester Epidemiology Project (REP) (see Figure 1). The REP is a population-based medical records-linkage system established in 1966. From 1966 through 2010, the REP was restricted to residents living in Olmsted County, Minnesota. In 2010, the REP expanded to include people residing in a 27-county region of southern Minnesota and western Wisconsin (Rocca et al., 2018). The REP captures full-text, person-level inpatient, outpatient, and emergency department data on all medical conditions seen by participating providers in the above described geographic regions, regardless of age, sex, ethnicity, socio-economic or insurance status. The REP's data linkage methods have been validated and have shown high sensitivity (ability to correctly link records that belong to the same person) and specificity (ability to correctly exclude linkage of records not belonging to same person) (St Sauver, Grossardt, Yawn, Melton, & Rocca, 2011). In 2010, the core 8-county REP had a 96.2% coverage of the U.S. Census population for that geographic region. The REP is considered one of the foremost population-based research resources worldwide (St Sauver et al., 2012).

We identified all subjects where a diagnosis of EDS was mentioned in the medical record for the time period January 1, 1976 – December 31, 2015 using the following code types: HICDA (Hospital Adaptation of the International Classification of Diseases) code: 07598110 for the period 1976–2010; ICD-9 (International Classification of Disease, Ninth Edition): 756.83 for the period 1995–2015; and ICD-10 (International Classification of Disease, Tenth Edition): Q79.6 for the period 10/1/2015–12/31/2015. Subjects were eligible for inclusion if they were born in and had resided and received care in the REP geographic region for at least their first year of life. Medical records were reviewed to classify the sub-type and validity of the EDS diagnosis, based upon history, clinical examination, Beighton score (a 9-point scale that measures joint hypermobility), and other diagnostic and genetic data. Given the retrospective nature of this study, validation was limited by the available information. We developed the following classification scheme for this study: *Confirmed EDS*: meets criteria present in the *2017 International Classification of the Ehlers-Danlos Syndromes* (Malfait et al., 2017) plus identification of a causative genetic variant(s), or in the case of hypermobile EDS (for which there is no currently known genetic variant), all three criteria listed in the 2017 International Classification present; *Probable EDS*: criteria present as outlined in the *2017 International Classification of the Ehlers-Danlos Syndromes*, but no causative genetic variant(s) found or testing not done; in the case of hypermobile EDS, diagnosis strongly suspected by medical geneticist or similar subspecialist with

expertise in musculoskeletal disorders and meets 2 of the 3 criteria listed in the 2017 International Classification; *Possible EDS*: diagnosis reported on multiple occasions over time in medical records but only partially meets criteria listed in the 2017 International Classification. Demographic information on subjects with EDS was extracted from the electronic and paper records. Data were collected and managed using REDCap hosted at Mayo Clinic (Harris et al., 2009).

We used a case-control study design with a 3:1 control: case match. Controls were randomly selected through the REP matching tool based on birth date, gender, residency at index date (first EDS billing code date of case at a REP facility), registration date, and last follow up date. Birth date, residency at index date, and last follow up date were matched +/− 1 year.

Exclusion criteria included having a genetic or metabolic condition other than EDS, any chronic medical condition acquired during the first 18 years of life linked to osteopenia, use of medications during the first 18 years of life associated with osteopenia, or gestational age < 38 weeks.

Case and control electronic and paper records were reviewed by M.C.R. and C.D. for any fracture diagnosis from birth through 18 years of age. Fractures were characterized by age at time of injury, location, fracture type, and mechanism. We assessed records for any radiologic mention of osteopenia or metabolic bone disease.

Statistical Analysis

We used the standardized difference (s.d.) to measure the amount of balance between the case and control groups for the matching criteria. The s.d. is not affected by sample size, and as a general rule of thumb, an s.d. less than 0.1 can be considered negligible (Austin, 2011).

Our primary outcomes of interest were the fracture rates during infancy (birth −1 year) and childhood (birth – 18 years). To account for matching, we used conditional logistic regression to assess the association of childhood fractures and EDS. An alpha level of .05 was used to determine statistical significance.

The study was approved by the Mayo Clinic Institutional Review Board.

RESULTS

A total of 219 potential EDS cases were identified by diagnostic codes between 1976 – 2015 out of the 156,760 subjects in the 2015 REP census. 174 of these (79.4%) were excluded due to not having medical records for the first year of life in the REP. Another 18 (8.2%) were excluded due to inability to reasonably confirm a diagnosis of EDS (reasons for exclusion included: insufficient clinical information in medical record to substantiate a diagnosis; condition excluded by medical genetics; condition only briefly mentioned in medical record with no further evaluation; or subject felt to have another diagnosis). Six of the remaining 27 subjects (2.7%) were excluded after close review of their medical records failed to identify sufficient clinical criteria to support classification as confirmed, probable or possible EDS cases. Of the remaining 21 cases, there were 14 hypermobile, 2 classical, 4 vascular and 1 arthrochalasia subtypes of EDS. Eleven of 14 (79%) hypermobile cases had sufficient

findings documented in the EMR to be considered probable (5/14) or confirmed (6/14) cases based upon the criteria listed above; 3 of 14 (21%) were considered possible cases. All 4 subjects with vascular EDS were confirmed by both clinical features and molecular testing; both subjects with classical EDS were felt to be probable cases, meeting clinical criteria but lacking molecular testing; the one subject with arthochalasia EDS was felt to be a probable case with multiple consistent clinical findings and a positive skin biopsy but no molecular testing.

The s.d. between cases and controls was < 0.1 for all demographic and matching variables (Table 1).

Eleven of 21 EDS cases (52.4%) had one or more fractures during the first 18 years of life. Three cases (14.3%) had more than one fracture during childhood. Six of 14 (42.8%) cases with the hypermobile EDS subtype had at least one fracture during childhood. Three of the four cases (75%) with vascular EDS and both cases (100%) with classical EDS had at least one fracture. The subject with arthrochalasia EDS had no fractures. Fractures identified in cases included long bone, clavicle, and hand or finger fractures; a 17 year-old subject involved in a motor vehicle accident suffered a vertebral compression fracture. All fractures were felt to be acute. The mechanism of injury in all of the fractures among the cases was felt to be accidental. Table 2 details age at time of fracture, fracture location, reported mechanism, and EDS subtype for all cases having fractures.

Fifteen of 63 matched controls (23.8%) had one or more fractures between birth and 18 years of age. Four control subjects (6.4%) had more than one fracture during childhood. Fractures in control subjects included long bone, hand or finger, nasal, and skull fractures; a 12 year-old subject suffered two posterior rib fractures following a motor vehicle accident. All fractures were felt to be acute. The mechanism of injury in all of the fractures among the control subjects was felt to be accidental. There were no fractures identified in either cases or controls in the first year of life. Table 3 shows summary statistics on fracture incidence and age at time of first fracture for cases and controls.

Comparing cases to controls, we found that EDS was associated with having any fractures during childhood with an odds ratio of 3.4 (95% CI: 1.20 – 9.66).

DISCUSSION

In this retrospective, population-based case-control study, subjects with the three most common forms of EDS (hypermobility, classical and vascular) had fractures more frequently identified during childhood, when compared to an age- and gender-matched control group. However, the fractures seen in the EDS cases were found only among subjects old enough to be ambulatory, and were those typically seen following common childhood accidental events and similar in type to those found in the control subjects. We found no evidence that subjects with EDS are predisposed to more frequent fractures during infancy.

To our knowledge, our study is the first population-based, case-control study to investigate fracture incidence during infancy and childhood among subjects with EDS. The literature on this topic is limited and conflicting, with existing studies largely confined to adult subjects,

generally lacking controls, or having major methodological flaws. A 1969 report on 100 subjects with EDS did not find any increased incidence of bone fragility (Beighton & Horan, 1969), however no control group was reported nor were subject demographics described. Dolan et al. studied 23 adult subjects with EDS (mean age 38.5 years (range 18–64)) who were compared to 23 age-matched controls (Dolan, Arden, Grahame, & Spector, 1998). Fractures were 10 times more common in the EDS group (87% vs. 8.7%). Significant decreases in bone density as measured by DXA scan were found at both the lumbar spine and femoral neck, however another study (Carbone et al., 2000) on the same number of subjects and controls failed to replicate these results. Yen et al studied a convenience sample of 16 subjects with EDS between the ages of 1.5 to 36 years. The authors mention fractures in 3 of the 16 subjects but provide no further description about age at time of fracture, fracture location, or trauma history, nor was there a comparison group (Yen, Lin, Chen, & Niu, 2006). More recently, Stern et al. reported on musculoskeletal findings in 205 clinic-identified 6–19 year-old subjects with EDS seen over a 5-year period (Stern et al., 2017). The majority of these (55.6%) had hypermobile EDS. Of the 205 subjects, 30 (14.6%) had 56 traumatic fractures identified. Unfortunately, no comparison group was included, no details were provided about fracture type, and subjects younger than age 6 were not addressed.

In 2017, Hollick et al. reported on a specialty clinic referral sample over 6 years of 72 infants less than 1 year of age with multiple fractures originally attributed to physical abuse (Holick et al., 2017). The authors report that the cases were referred for a second opinion, and screened prior to agreement to their evaluation. Of these 72 infants, 67 (93%) were reported to have EDS and 5 (7%) were reported to have vitamin D deficiency and clinical or radiologic evidence of rickets. Mean age at time of initial fracture was 12 +/− 8.4 weeks. Specific fractures reported in the EDS cases included ribs (58%), femur (36%), humerus (24%), tibia (33%), corner metaphyseal lesions (16%) and scapula, pelvic, radius, ulna, fibula and metatarsal fractures in 28%. Although criteria for the clinical diagnosis of EDS in infants does not exist (Shur & Carey, 2015), the majority of infants were felt by the authors to have hypermobile EDS, based upon either a family history of hypermobility in one of the parents or the presence in the infants of 10 clinical features that the authors considered diagnostic of EDS. However, the authors provide no details about what number or combination of these 10 features constitute a diagnosis of EDS, and only 3 of the reported 10 are listed as signs of hypermobile EDS in the *2017 International Classification of the Ehlers-Danlos Syndromes*. Of the 43 parents who reported a family history of hypermobility and whose infants were evaluated, data regarding Beighton score was available only for 19 (44%). Of the 67 infants reported in the paper to have EDS, only 43 (64%) were directly examined by the authors. Additionally, although the authors acknowledge that it is not possible to perform a Beighton score on an infant, they report that 100% of the 43 infants examined had hypermobility/flexibility. The authors cite 7 references (Abtahi-Naeini, Shapouri, Masjedi, Saffaei, & Pourazizi, 2014; Ayoub, Hyman, Cohen, & Miller, 2014; Cannell & Holick, 2018; Keller & Barnes, 2008; Owen & Durst, 1984; Paterson, 2009; Roberts et al., 1984) in support of their statement that "…rickets and Ehlers-Danlos/ hypermobility syndrome (EDS), which are associated with normal or low bone density and increased bone fragility, can also result in X-ray findings that can be mistaken for child

abuse" (Holick et al., 2017) (p. 1), however a close review of these papers does not support this statement. In summary, the paper, while purporting to establish hypermobile EDS as a cause of fractures during infancy misinterpreted as being due to non-accidental trauma, suffers from multiple methodological issues that raise concern about its conclusions.

One of our subjects had a rare form of EDS, the arthrochalasia subtype, although the subject had no fractures identified during childhood. This subtype and a few other rare forms of EDS-like conditions (e.g. the EDS/ Osteogenesis Imperfecta (OI) overlap syndromes and several linkeropathies) do appear to have increased fracture susceptibility, sometimes with histories of little or no trauma (Colombi, Dordoni, Chiarelli, & Ritelli, 2015; Giunta, Superti-Furga, Spranger, Cole, & Steinmann, 1999; Jones, Schwarze, Adam, Byers, & Mefford, 2015; Malfait et al., 2013), however the additional associated clinical features of these conditions should allow them to be distinguished readily from cases of suspected non-accidental trauma. Aside from these conditions, only the Holick et al. study cited above has shown an increased number of fractures in infants with the more common forms of EDS. Therefore, to quote Castori, "the hypothesis of Ehlers-Danlos syndrome as an alternative explanation for infantile fractures remains speculative" (Castori, 2015) (p. 289), and our study results provide further confirmation of this statement.

Our study did identify a higher incidence of fractures in older, ambulatory children with the most common forms of EDS. While our study design does not allow us to infer causality, there are theoretical reasons why EDS might be associated with a predisposition to fracturing in older, ambulatory children. For example, some have hypothesized that complications of EDS may be secondary to proprioceptive deficits (Clayton, Jones, & Henriques, 2015); others have speculated that joint hypermobility syndrome or hypermobility EDS may confer a neurodevelopmental profile affecting coordination, presumably leading to more fractures of accidental etiology (Ghibellini, Brancati, & Castori, 2015). However, until replicated in a larger, prospective study, our findings should be interpreted as preliminary and with caution.

Strengths of this study include the population-based design, inclusion of a closely matched control group, and restriction of EDS cases to those with substantial clinical evidence for the condition. Study limitations include, most significantly, the small sample size, a consequence of our requirements for first year of life medical records, diagnostic validity, and the low population prevalence of EDS. Additional limitations include the lack of complete clinical information on some subjects given the retrospective design, and the historical nature of the study encompassing timeframes when there may have been a higher threshold to obtain diagnostic imaging and less recognition and understanding of non-accidental injuries. Finally, we recognize that our results may be confounded by unmeasured variables (e.g. caregiver health care-seeking behavior), which could lead to increased fracture identification in children diagnosed with EDS.

Conclusions

We found no evidence that subjects with common forms of EDS have increased fracture susceptibility during infancy. Ambulatory subjects with these EDS subtypes may have a higher incidence of fractures during childhood.

Acknowledgements

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WHAT IS KNOWN

Ehlers-Danlos syndrome (EDS), an inherited connective tissue disorder, has been proposed as a cause of unexplained fractures during infancy that may mimic non-accidental injury, despite little evidence in the medical literature to support this conclusion.

WHAT THIS STUDY ADDS

In this population-based, case-control study, we found no evidence that infants with common forms of EDS are predisposed to more frequent fractures. We did identify a higher incidence of fractures in older, ambulatory children with these EDS subtypes.

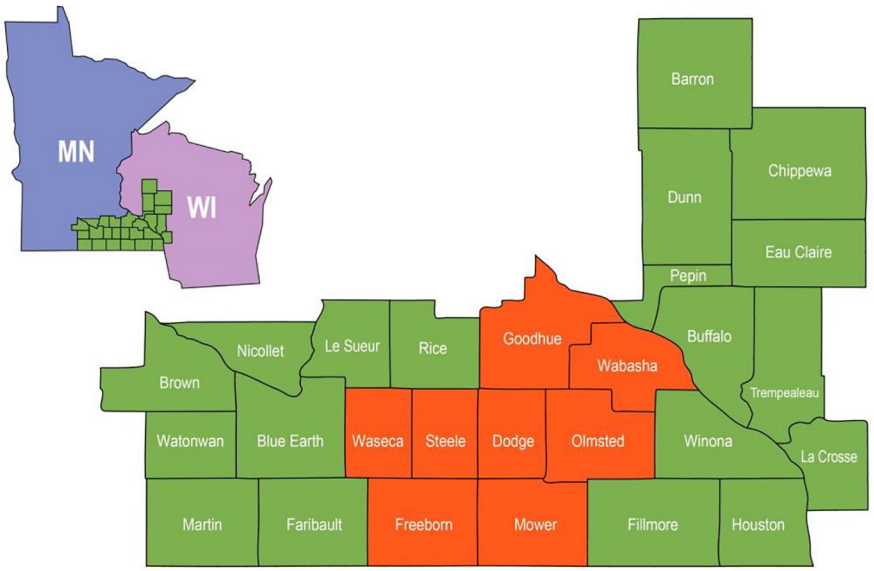

Figure 1.

Geographic map of counties in Rochester Epidemiology Project (core 8-county region in Minnesota highlighted in orange). Adapted from: (Rocca et al., 2018).

Table 1.

Demographic characteristics and matching variables for cases and controls

	Controls (N=63)	Cases (N=21)	Standardized Difference
Birth Year			−0.005
Median	1976	1976	
Range	1947 – 1999	1948 – 1998	
Female Gender	45 (71.4%)	15 (71.4%)	0.000
Registration Year			0.004
Median	1976	1976	
Range	1947 – 1999	1948 – 1998	
Age at Index (yrs)			−0.001
Mean (SD)	25.7 (13.2)	25.7 (13.3)	
Range	0.6 – 52.7	1.4 – 51.9	
County at Index			0.000
Dodge, MN	3 (4.8%)	1 (4.8%)	
Olmsted, MN	54 (85.7%)	18 (85.7%)	
Wabasha, MN	6 (9.5%)	2 (9.5%)	
Age at Last Follow Up (yrs)			−0.019
Mean (SD)	38.7 (16.2)	38.4 (15.9)	
Range	17.7 – 66.5	19.3 – 65.3	

Table 2.

EDS Subtypes and Fracture Details for Identified Cases

Subject No.	EDS Subtype	Age at Time of Fracture (yrs)	Fracture Location	Medical Record Documentation of Injury Mechanism
4	Vascular	3.7	Radius/ulna	Fall
		14.6	Radius	Skiing, fall
6	Vascular	4.9	Finger	Fall
9	Classical	5.1	Supracondylar	Jumping on bed, fall
		10.6	Lateral epicondyle	Rollerskating
10	Vascular	12.3	Clavicle	Bicycle accident
11	Hypermobile	11.5	Fibula	Stumble on stairs
12	Hypermobile	1.5	Radius/ulna	Struck by Bicycle
13	Hypermobile	16.7	Fibula	Fall
14	Hypermobile	1.9	Radius/ulna	Fall
15	Classical	3.2	Clavicle	Fall from swing
		12.3	Tibia	Jumping on trampoline, fall
17	Hypermobile	12.6	Metacarpal	Struck against wall
18	Hypermobile	17.4	Radius; T12-L2 vertebral compression	MVA

Table 3.

Summary statistics for fractures among cases and controls

	Controls (N=63)	Cases (N=21)
Number of Childhood Fractures		
0	48 (76.2%)	10 (47.6%)
1	11 (17.5%)	8 (38.1%)
2	3 (4.8%)	3 (14.3%)
3	1 (1.6%)	0 (0.0%)
Age at First Fracture		
Infant (<1)	0 (0.0%)	0 (0.0%)
1 – 5	3 (20.0%)	6 (54.5%)
6 – 10	5 (33.3%)	0 (0.0%)
11 – 17	7 (46.7%)	5 (45.5%)